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Endocrine manifestations in a cohort of 63 adulthood and childhood onset patients with Langerhans cell histiocytosis

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Abstract

Objective: Langerhans cell histiocytosis (LCH) is a rare inflammatory myeloid neoplasm which can infiltrate any organ or tissue. Endocrine involvement has mostly been described in case reports and small retrospective studies. We aimed to describe endocrine manifestations in a large cohort of adulthood onset (AO) and childhood onset (CO) patients with LCH.

Design: Single-center observational study conducted between January 2002 and December 2017 at Pitié-Salpêtrière University Hospital (Paris, France), a tertiary care hospital.

Method: Clinical, biological and morphological evaluations of pituitary, gonadal, adrenal and thyroid function evaluations performed in 63 consecutive patients with LCH (AO patients: 40, CO patients: 23). Fifty-eight patients underwent follow-up assessments.

Results: Complete pituitary evaluation was performed in 38/63 patients (60.3%); at least one anterior pituitary dysfunction (APD) was found in 63.2% of them. In this subgroup of patients, the most prevalent deficiencies were diabetes insipidus (DI) and GHD (55.3% each), followed by gonadotropin deficiency (34.2%) and thyrotropin deficiency (23.7%). In the subgroup of the 25 incompletely evaluated patients, we found DI in 44%, GHD in 50%, gonadotropin deficiency in 30.4% and thyrotropin deficiency in 16%. APD was more common in CO patients ($P = 0.003$) but was not systematically associated with DI regardless of the age of onset. Endocrine dysfunction was most often permanent; moreover, occurrence of new deficiencies has been described during follow-up.

Conclusion: The spectrum of endocrine disorders appears to be large in LCH (both in AO and CO patients) and should be evaluated carefully at diagnosis and during follow-up. APD was not always associated with DI.

Introduction

Langerhans cell histiocytosis (LCH) is a rare inflammatory myeloid neoplasm that can infiltrate any organ or tissue of the body (1). It is the most common histiocytic disorder, characterized by CD1a and/or Langerin (CD207)-positive cells on immunostaining that are required for definitive diagnosis (2, 3). Its pathogenesis is still not precisely defined; a clonal component along with a frequent BRAFV600E mutation have been identified, indicating that LCH is a disorder that is more neoplastic than reactive (3).

Initially described in childhood onset (CO) disease, it is now increasingly recognized in AO cases.

The clinical presentations of LCH vary from clinically self-limiting lesions that resolve spontaneously to rapidly progressive disease that requires systemic chemotherapy. Any organ or system of the human body can be affected, but those most commonly involved in children are bones (80% of cases), skin (33%), pituitary gland (25%), liver, spleen, hematopoietic system and lungs (15% each), lymph nodes (5–10%) and central nervous system excluding the pituitary gland (2–4%). In adult patients, the lungs are most commonly affected (4, 5, 6).

The current classification differentiates between lung LCH or single system LCH (SS-LCH: only one organ or system is involved, such as one or more bones, skin, lymph nodes, the hypothalamic–pituitary/central nervous system, lungs in adults) and multisystem disease (MS-LCH: two or more organs or systems are involved, with or without involvement of risk organs) (7).

Treatment options vary depending on the extent of the disease and the severity at onset. The current standard of care, based on LCH III, is 1 year of therapy with vinblastine and prednisone, plus mercaptopurine for patients with high-risk disease (8).

Endocrine manifestations have been described in LCH in a few case reports and in small retrospective AO series (9, 10). In 2016, the French national CO LCH patients registry had 1478 patients, of whom 223 (15%) had an endocrine manifestation, though evaluations were only done when there was a suspected endocrine abnormality (11). Infiltration of the hypothalamo-pituitary axis leading to diabetes insipidus (DI) is the main known endocrine symptom of LCH in about 15–25% of CO and 12–30% of AO patients. Anterior pituitary dysfunction is found in up to 20% of patients with LCH and is almost always associated with DI. Growth hormone (GH) deficiency is the most common anterior pituitary hormone deficiency, followed by adrenocorticotropin (ACTH) deficiency,

thyroid-stimulating hormone (TSH) deficiency and hyperprolactinemia (9).

There seems to be no information about the prevalence of bone metabolism disorders in AO disease, but there are several predisposing factors, such as inflammatory cytokines, anterior pituitary hormone deficiencies and treatment with glucocorticoids in particular.

To date, no comprehensive investigation of the endocrine manifestations has been conducted in a large cohort study. We thus decided to perform hormonal evaluations on all consecutive patients diagnosed with LCH with or without known endocrine dysfunction (ED) referred to our department. Our aims were to determine the prevalence of endocrine manifestations in LCH and to describe their evolution during follow-up.

We present 15 years of experience from this first single-center study evaluating the endocrine features of AO and CO LCH in our cohort.

Patients and methods

This was a single-center observational study conducted from January 2002 to December 2017 and included all patients (CO and AO) diagnosed with LCH at La Pitié-Salpêtrière-Charles Foix University Hospital (Paris, France). Patients could have been managed in the department of endocrinology or those of internal medicine and neurology.

We first listed all patients followed for histiocytosis disorder. Then, based on histological proof and/or typical lesions, we excluded the other types of histiocytosis to include only LCH (Fig. 1). Most CO LCH patients were received as part of transition to adult health care and had already some known ED. The distinction between CO and AO was made using the age of first signs of LCH, with a cut-off age of 18 years.

An endocrine evaluation was proposed for all consecutive patients in the department of endocrinology and reproductive medicine. Those in whom this was not possible underwent an endocrine evaluation in the internal medicine department or in the department of neurology. Patients in the internal medicine and/or neurology and/or endocrinology and reproductive medicine departments had endocrine reevaluations during follow-up. Data were collected retrospectively and we only reported evaluations done in these departments. We distinguished our patients in two subgroups, one with patients with complete endocrine evaluation and the other one including patients with incomplete endocrine evaluation.

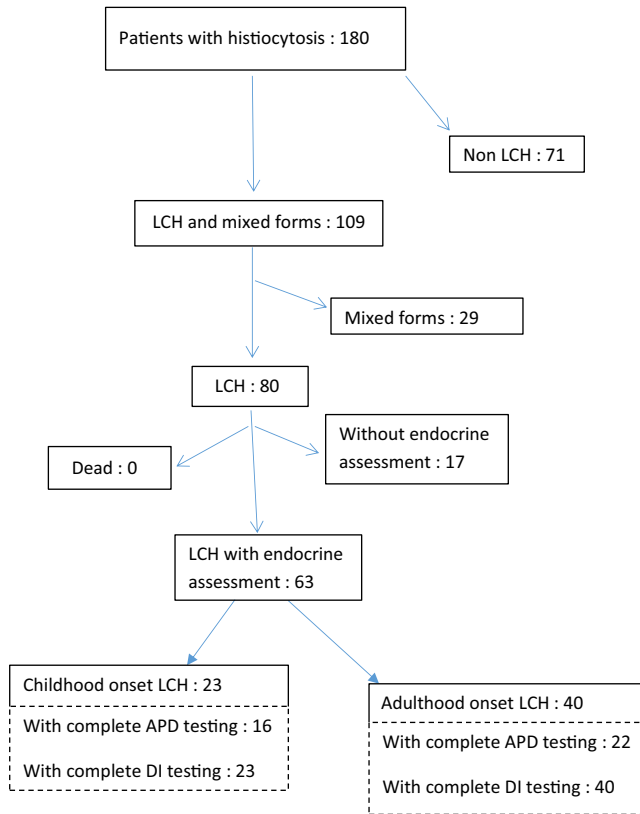


Figure 1

Flow chart to indicate how subjects were selected for inclusion in the study. APD, anterior pituitary deficiency; DI, diabetes insipidus; LCH, Langerhans cell histiocytosis.

Data collection

Data were collected from hospital patient medical records.

The following data were recorded: age at diagnosis of LCH and age at first clinical signs, age at first endocrine signs, endocrine involvement known before the assessment.

Clinical examination data included, 24-h evaluation of water intake and diuresis, thyroid examination and breast and genital examination.

Hormonal assays were performed to explore pituitary and peripheral gland function as follows:

- Patients were considered to have DI if they were already being treated with desmopressin or if they had a polyuria–polydipsia syndrome responding to desmopressin treatment following a water deprivation test (12).
- Gonadotropin and gonadal functions were evaluated based on FSH and LH in all patients, estradiol (E2), in women and total testosterone in men.

Central hypogonadism was defined in men by the presence of low testosterone levels with the absence of increased gonadotropins. In premenopausal females the diagnosis of central hypogonadism was defined by the presence of oligomenorrhea/amenorrhea (after exclusion of other causes of menstrual irregularity) in addition to low estrogens and gonadotropin levels. In postmenopausal women, the absence of high serum FSH and LH was sufficient for a diagnosis of gonadotropin dysfunction (13).

- Thyrotropin function and thyroid function were evaluated based on the TSH, free T4, free T3 and anti-thyroid peroxidase (ATPO) and antithyroglobulin (ATG) antibody concentrations. Central hypothyroidism was characterized by an FT4 level below the laboratory reference range in conjunction with a low, normal or mildly elevated TSH (13).
- Lactotropin function was evaluated based on prolactin (PRL) concentration. Hyperprolactinemia was defined when PRL was $>25\mu\text{g/L}$ in women and $>20\mu\text{g/L}$ in men (14).
- Corticotropin insufficiency was defined by a plasma cortisol level of $<3\mu\text{g/dL}$, a response to an insulin tolerance test (ITT) or 0.25 mg of Synacthen of $<18\mu\text{g/dL}$ for plasma cortisol and $<1.3\mu\text{g/dL}$ for salivary cortisol, associated with normal or low ACTH. Adrenal glucocorticoid insufficiency was defined by the same thresholds for cortisol as those associated with elevated ACTH (15, 16).
- Somatotropin function was evaluated based only on the IGF-I and GH concentrations under stimulation by an ITT, when possible. According to guidelines (13, 17, 18, 19), GH deficiency (GHD) was defined in adults by a peak GH concentration $<5\mu\text{g/L}$ after a stimulation test (severe GHD was defined as a peak GH concentration of $<3\mu\text{g/L}$, and partial GHD was defined as a peak GH concentration between 3 and $5\mu\text{g/L}$). In children, a GH peak concentration below $4\mu\text{g/L}$ ($5\mu\text{g/L}$ in transition period) defined complete GHD and a peak between 4 and $7\mu\text{g/L}$ indicated partial GHD (20, 21, 22, 23). A second GH stimulation test was not performed to confirm diagnosis when GHD was isolated. The IGF-I concentrations was evaluated using normal age-related reference concentrations (24).

Bone metabolism was assessed based on the serum calcium, serum phosphorus, PTH1–84 and 25-hydroxyvitamin D concentrations.

The following radiological examinations were performed: pituitary magnetic resonance imaging

(MRI), pelvic ultrasound, thyroid ultrasound and bone mineral density (BMD) assessment by dual-energy X-ray absorptiometry (DEXA). In postmenopausal women and in men aged 50 and older, osteoporosis was diagnosed if the T-score of the lumbar spine, total hip or femoral neck was -2.5 or less. In females prior to menopause and in males younger than age 50 years, a Z-score of -2.0 or lower was defined as 'below the expected range for age,' and a Z-score above -2.0 was 'within the expected range for age' (25).

Assay methods

Blood tests were performed at 08:00h, and hormonal assays were processed in the biochemical and hormonal department of Pitié-Salpêtrière Hospital. FSH, LH, E2, progesterone, total testosterone, prolactin, ACTH, plasma cortisol, TSH, T4L, T3L and PTH (1–84) were measured according to the Modular E170 chemiluminescence method (Roche Diagnostics). In patients with hyperprolactinemia, we used polyethylene glycol precipitation to detect macroprolactinemia. GH, IGF1, aldosterone, renin and 25-OH vitamin D were measured by a chemiluminescence method (Liaison XL Diasorin, Vercelli, Italy). D-4 androstenedione was measured by an extraction method+RIA IM0674 (Beckman Coulter), DHEA-S was measured by chemiluminescence (Access, Beckman Coulter), ATG and ATPO antibodies were measured by Phadia 250 EliA.

Ethical consideration

This is a retrospective observational study. By French law, no IRB advice was required to conduct this study.

Statistical analysis

Continuous variables are expressed as a mean \pm standard deviation (s.d.) and compared by Student's unpaired, two-sided *t*-test.

Categorical variables are presented as percentages and compared using the chi-square (χ^2) test or the Fisher's exact test.

All reported *P* values are two-sided. *P* values <0.05 were considered statistically significant.

The statistical analyses were performed using Predictive Analytics Software (PASW Statistics) version 18.

Results

From January 2002 to December 2017, 63 patients (40 AO with 15 males and 23 CO with 12 males) with LCH were followed at Pitié-Salpêtrière hospital with endocrine assessments (Fig. 1). Seventeen patients followed in the department of neurology had no endocrine assessment and were excluded from the study.

All of the 63 included patients did not have a complete endocrine evaluation for many reasons:

- concerning corticotropin function, it was not evaluated in five patients under treatment with corticosteroids for LCH at the time,
- concerning gonadotropin function, prolactinemia, GH stimulation test, we did not obtain data respectively in 2, 4 and 23 patients, mainly because of the management of those patients in departments with lower practice of endocrinological tests.

Complete anterior pituitary evaluation was obtained in 38 patients (60.3%).

The baseline characteristics of all patients with LCH are summarized in Table 1. The mean time between the first clinical signs and the diagnosis of LCH was 1.7 years for AO and 1.6 years for CO patients. Eighteen of the 40 AO patients and 14 of the 23 CO patients had MS-LCH.

The BRAF status was evaluated for LCH lesions in 14 patients (22.2%) and a BRAFV600E mutation was identified in 3 cases (21.4%).

Twelve of the 40 AO patients and 18 of the 23 CO patients had known ED before evaluation ($P=0.006$); this mostly concerned DI in 27 patients.

Pituitary and peripheral gland function

Considering the 38 patients with complete evaluation, 24 patients (63.2%, including 50% of AO LCH and 81.2% of CO forms) had at least one anterior pituitary dysfunction (APD, Table 2): 8 (22.2%) had 2 APDs, 5 (13.9%) had 3 APDs and 5 others (13.9%) had 4 APDs. In this subgroup, an ED was the first sign of LCH in 36.8% patients (14 of 38). Overall, the first ED was DI in 47.4% of patients (18 of 38), growth deficiency in 13.2% (5 of 38), gonadotropin deficiency, hyperprolactinemia and thyrotropin deficiency in 2.6% each (1/38).

For the other 25 patients, 12 (48%) had at least one APD (Table 2). Among them, an ED was the first sign of LCH in 12% patients (3 of 25); and the first endocrine dysfunction was DI in 36% of patients (9 of 25),

Table 1 Baseline characteristics of patients with LCH at their first endocrine evaluation.

	Adulthood onset	Childhood onset	P value
Age at diagnosis, years (median/min-max)	34 (19, 87)	4 (0, 23)	-
Origin			
Caucasian	9	6	-
Unknown	30	16	-
Afro-American	1	1	-
Age at first clinical signs of LCH, years (median/min-max)	32.5 (18-87)	4 (0-17)	-
Time before diagnosis, years (mean/min-max)	1.7 (0-12)	1.6 (0-12)	-
Type of LCH (%)			
Single systemic LCH	22/40 (55)	9/23 (39.1)	0.341
Multisystemic LCH	18/40 (45)	14/23 (60.9)	0.341
Type of involvement (%)			
Skeletal	24/40 (60)	15/23 (65.2)	0.887
Unifocal	15/24 (62.5)	9/15 (60)	0.878
Multifocal	9/24 (37.5)	6/15 (30)	0.878
Pulmonary	20/40 (50)	9/23 (39.1)	0.421
Cutaneous	9/40 (22.5)	11/23 (47.8)	0.046
Mucous	3/40 (7.5)*	0/23	0.293
Central nervous system**	3/40 (7.5)	9/23 (39.1)	0.005
Hematological	0/40	3/23 (13)	0.045
Lymph node	2/40 (5)	0/23	0.529
Hepatic	0/40	3/23 (13)	0.045
Intestinal	2/40 (5)	0/23	0.529
Histological proof of LCH (%)	39/40 (97.5)	23/23 (100)	-
BRAF status performed (%)	9/40 (22.5)	5/23 (21.7)	-
Positive	1/9 (11.1)	2/5 (40)	-
LCH disease activity at the time of endocrine evaluation			
Non-active disease	20/40 (50)	9/23 (39.1)	0.568
Stable disease	9/40 (22.5)	2/23 (8.7)	0.301
Regressive disease	5/40 (12.5)	10/23 (43.5)	0.013
Progressive disease	6/40 (15)	2/23 (8.7)	0.699
Toxics			
Tobacco	25/40 (62.5)	13/23 (56.5)	0.841
Alcohol	2/40 (5)	3/23 (13)	0.345

*All genital, **other than hypothalamo-pituitary involvement.

gonadotropin deficiency in 4.3% (1 of 23) and hyperprolactinemia in 4.8% each (1 of 21).

We thus found ED in nine patients who had no suspected endocrine abnormality: 6 in the 38 completely evaluated patients (15.8%) and 3 in the 25 others (12%).

Diabetes insipidus

DI was found in 21 of the 38 completely evaluated patients (55.3%) and in 11 of the 25 others (44%). It was more significantly found in CO than AO disease ($P=0.006$). It was found in 13 of the 31 patients (41.9%) with SS-LCH and 19 of the 32 patients (59.4%) with MS-LCH, but this difference was not significant ($P=0.26$).

Somatotropin function

A GH stimulation test by ITT was performed in 40 patients.

It revealed GHD in 21 of the 38 completely evaluated patients (55.3%) and 1 among the 2 other patients; the frequency was not different between CO and AO disease ($P=0.1$). Four of the GHD adult patients were obese.

The IGF-I level was evaluated in all the 38 completely evaluated patients and 13 of them (34.2%) had a level <-2 SD. It was also evaluated in 15 of the other patients in whom 3 (20%) had a level <-2 SD.

All the 22 patients with GHD had an IGF-I level <-1 SD and 13 of them had a level <-2 SD.

Corticotropin function

The pituitary-adrenal axis was evaluated in 58 patients and was normal in 81% of them. Corticotropin deficiency was found in 8 of the 38 completely evaluated patients (21%) and 3 in the 20 others (15%), all with a history of

Table 2 Frequency of endocrine dysfunctions in patients with LCH.

Hormonal dysfunction	% of patients (n/N)		P value
	Adulthood	Childhood	
Age at first endocrine signs, years (median/min–max)	31.5 (18–58)	6 (2–23)	–
Age at first endocrine evaluation, years (median/min–max)	39 (20–88)	20* (14–62)	–
Known endocrine dysfunction before evaluation	12/40 (30)	18/23 (78.3)	0.000
DI	10/40 (25)	17/23 (73.9)	0.000
At least 1 APD	7/40 (17.5)	13/23 (56.5)	0.003
At least 1 APD without DI	1/40 (2.5)	1/23 (4.3)	0.730
<i>Patients with complete evaluation</i>	<i>55 (22/40)</i>	<i>69.6 (16/23)</i>	–
Endocrine dysfunction	50 (11/22)	93.7 (15/16)	0.005
Diabetes insipidus	36.4 (8/22)	81.2 (13/16)	0.008
At least 1 APD	50 (11/22)	81.2 (13/16)	0.08
GH deficiency	45.4 (10/22)	81.2 (11/16)	0.2
Partial	40 (4/10)	27.3 (3/11)	0.659
Severe	60 (6/10)	72.7 (8/11)	0.659
Hyperprolactinemia	22.7 (5/22)	18.7 (3/16)	0.546
Gonadotropin deficiency	31.8 (7/22)	37.5 (6/16)	0.746
Central deficiency	100 (7/7)	100 (6/6)	–
TSH deficiency	18.2 (4/22)	31.2 (5/16)	0.449
Corticotropin deficiency	13.6 (3/22)	31.2 (5/16)**	0.243
<i>Patients with incomplete evaluation</i>	<i>45 (18/40)</i>	<i>30.4 (7/23)</i>	–
Endocrine dysfunction	50 (9/18)	71.4 (5/7)	0.406
Diabetes insipidus	38.9 (7/18)	57.1 (4/7)	0.656
At least 1 APD	38.9 (7/18)	71.4 (5/7)	0.201
GH deficiency	NA	50 (1/2)***	–
Hyperprolactinemia	25 (4/16)	20 (1/5)	0.948
Gonadotropin deficiency	25 (4/16)	42.8 (3/7)	0.625
Central deficiency	75 (3/4)	100 (3/3)	–
Peripheral deficiency	25 (1/4)	0	–
TSH deficiency	0	57.1 (4/7)	0.062
Corticotropin deficiency	7.1 (1/14)	33.3 (2/6)**	0.201

*Some of them had undertaken endocrine evaluations in childhood but here we just consider evaluations done in our department, **all after corticotherapy, ***complete GHD.

APD, anterior pituitary dysfunction; DI, diabetes insipidus; GH, growth hormone; NA, non-applicable, none was evaluated; TSH, thyroid-stimulating hormone.

corticosteroid treatment. No patient showed the features of adrenal glucocorticoid insufficiency.

Gonadotropin function

We found gonadotropin deficiency in 13 of 38 completely evaluated patients (34.2%), and in 7 of the 23 others (30.4%) with no difference between the CO and AO forms ($P=0.56$). We found a history of delayed puberty in five CO.

Eight women were postmenopausal. Among the 28 premenopausal women, 10 had regular menses, 11 had amenorrhea and the 7 other women had oligomenorrhea. Hormonal evaluation showed that the pituitary–gonadal axis was normal in 61.1% of the women. There was a gonadotropin deficiency in 7 of 23 completely evaluated women (30.4%, including 1 postmenopausal) and in 6 of the 12 others (50%).

We found one idiopathic ovarian insufficiency (46 XX, no anti-ovarian antibodies and no fragile X abnormality)

diagnosed at the age of 37 years and before the diagnosis of LCH. Pelvic ultrasounds were performed in 13 women and showed no abnormalities (in particular, no ovarian infiltration aside from one ovarian endometriosis).

In male patients, decreased libido was mentioned in 11.5% (3 of 26, all AO patients) and there was no erectile dysfunction. The hormonal evaluation showed gonadotropin deficiency in 40% of the completely evaluated men (6 of 15; 2 had decreased libido) and in 9.1% of the others (1 of 11); we did not find any testicular deficiency. There was no clinical testicular abnormality. Testicular ultrasounds were performed in five men and showed no abnormalities (in particular, no testicular infiltration).

Serum prolactin

Hyperprolactinemia was found in 21% of the completely evaluated patients (8 of 38) (Table 2), respectively 24% in

women and 18.5% in men. It was found in 5 of the 21 other patients (23.8%).

The PRL elevation was very mild in all patients: the mean PRL level in men was 31.7 ± 12 ng/mL and 32.3 ± 10.8 ng/mL in women. No use of treatments that induce hyperprolactinemia was reported. One woman had galactorrhea on the clinical examination. One man had bilateral gynecomastia with normal serum prolactin and two women had galactorrhea on the clinical examination.

Thyrotropin function

Nine of the 38 completely evaluated patients (23.7%) and 4 of the 25 others (16%) had thyrotropin deficiency (Table 2). It was more frequent in the CO form than in AO disease ($P=0.016$). Six patients had primary autoimmune hypothyroidism before the diagnosis of LCH and one other underwent a total thyroidectomy for a multinodular goiter (we excluded these patients from the thyroid evaluation).

Correlation between APD, LCH disease extension and DI

Considering patients with complete evaluation, an ED was found in 73.7% of patients with MS-LCH and 63.1% patients with MS-LCH, but this difference was not significant ($P=0.07$). Twenty-four of the 32 patients with DI (75%) had at least one APD. Among the 31 patients without DI, eight had at least one APD: six in the subgroup

Table 3 Frequency of pituitary and hypothalamic abnormalities at the magnetic resonance imaging (MRI) of patients with endocrine dysfunction.

	% of patients (n/N)	
	Adulthood	Childhood
Pituitary gland size		
Normal	80 (16/20)	84.2 (16/19)
Increased	10 (2/20)	0
Decreased	10 (2/20)	15.8 (3/19)
Thickness of the pituitary stalk		
Normal	75 (15/20)	68.4 (13/19)
Increased	20 (4/20)	15.8 (3/19)
Decreased	5 (1/20)	15.8 (3/19)
Hypothalamic region		
Infiltrated	5 (1/20)	15.8 (3/19)
Non-infiltrated	95 (19/20)	84.2 (16/19)
Absence of the physiological bright spot of the posterior pituitary	50 (10/20)	54.6 (12/19)

of completely evaluated patients (15.8%) and two in the others (8%).

Imaging

Twelve of the 61 patients who underwent a pituitary MRI showed a visible infiltrative lesion of the pituitary region or stalk (Table 3). Ten of them (83.3%) had pituitary deficiencies. The hypothalamic region was infiltrated in 9.6% of patients (6 of 61). Four patients with unsuspected endocrine deficiencies that were detected for the first time on screening had MRI abnormalities.

An absence of the physiological T1 bright spot in the posterior pituitary was found in 36.1% of patients, all of whom had DI. Nine patients with DI still had a visible physiological T1 bright spot in the posterior pituitary.

Bone evaluations

We found no abnormality in calcium metabolism, except in 1 of 62 assessed patients with moderately low calcium levels and 83.9% of patients (26 of 31) with low vitamin D levels.

Thirty-one patients (mean age=36 years) underwent a BMD assessment by DEXA. Four of them were postmenopausal women and we found osteoporosis and osteopenia in one case each (these two patients had gonadotropin deficiency and a history of corticotherapy). There were no men aged 50 and older among the patients who underwent a BMD assessment.

Among the 27 nonmenopausal women and men younger than age 50 years who underwent a BMD assessment, 4 (14.8%) had a Z-score below the expected range for age (one gonadotropin deficiency and two other after corticotherapy).

Evolution

Thirty-four patients (54%, 15 AO and 19 CO) required endocrine treatments.

Follow-up data were available for 58 patients (20 CO and 38 AO patients).

The mean follow-up time was 52.1 ± 43.5 months. Forty-eight patients underwent two endocrinological evaluations, and 35 patients underwent at least three assessments. The mean time between the first and the second evaluations and between the second and the third evaluations was respectively 1.3 and 2.7 years. Most of the pituitary deficiencies were permanent and some

Table 4 Follow-up data of 58 patients with LCH and endocrine dysfunction.

Endocrine dysfunctions	2nd evaluation, <i>n</i>			3rd evaluation, <i>n</i>		
	Disparition	Stable	New occurrence	Disparition	Stable	New occurrence
Hyperprolactinemia	3	5	0	1	4	4
Gonadotropin deficiency	2	14	2	3	13	0
GH deficiency	1	1	1	NA	NA	NA
Corticotropin deficiency	1	7	2	0	5	1
Thyrotropin deficiency	0	10	1	1	9	1
Diabetes insipidus	0	32	0	0	32	0

Mean time between the first and the second evaluation and between the second and the third evaluation: 1.3 and 2.7 years respectively.
GH, growth hormone; NA, not available.

that were not present at the first evaluation appeared progressively (Table 4).

Discussion

We report here a cohort of 63 consecutive patients with LCH who underwent endocrinological evaluations of pituitary, gonadal, adrenal and thyroid function. This study may have certain data limitations, such as the cross-sectional design that does not allow for a longitudinal evaluation to examine exactly how ED evolved over time. Moreover, for the CO LCH patients, we only included their data from our hospital. It is also possible that the 17 patients seen in neurology and excluded to this study could have had undiagnosed pituitary deficits. Finally, this study has other limitations that are a possible paucity of auxological and clinical data and difficulty in performing diagnosis of osteoporosis in young people.

Nevertheless, this study provides the first near-exhaustive investigation of endocrine and metabolic manifestations in LCH in a large cohort study.

ED was more prevalent in the CO forms than the AO forms. As previously reported, posterior pituitary dysfunction is a common endocrinological manifestation of LCH, and DI is usually the first endocrine manifestation (9, 10, 26, 27, 28, 29, 30). DI was the first endocrinological manifestation in 2.1% of CO patients in the French national LCH registry, but evaluations were not done systematically (31).

In our study, DI reached a prevalence of 55.3% in those with complete evaluation, and was similar to the one found in another recent study in a small population of adult pulmonary LCH patients with complete endocrine evaluations (10) but higher than the 30% described in previous studies (32, 33), even when considering our subgroup of incompletely evaluated. This prevalence has been described to possibly reach 40% in patients with MS-LCH or 94% in the presence of other pituitary

Table 5 Recommendations for endocrine assessment and surveillance protocol in patients with LCH.

	Clinical evaluation	Morphological evaluation	Biological evaluation
Pituitary	Search for signs of anterior pituitary deficits 24-h diuresis and water intake	Pituitary MRI	FSH, LH, E2 (women)/total testosterone (men) PRL TSH, FT4 IGF-1, GH under ITT ACTH, cortisol under ITT or after Synacthen test
Gonads			Natremia and urinary osmolarity FSH, LH, E2 (women), total testosterone (men)
Thyroid	Search for a goiter and nodules	Thyroid sonography if clinical anomalies	TSH, FT4
Adrenal glands	Search for signs of adrenal deficiency	Adrenal CT scan	ACTH, cortisol under ITT or after Synacthen test Renin, aldosterone
Follow-up	Every year	At any time if clinical or biological abnormalities	Every 3 years or at any time if clinical abnormalities

ACTH, adrenocorticotropin; CT, computed tomography; E2, estradiol; FSH, follicle-stimulating hormone; FT4, free T4; GH, growth hormone, IGF-1, insulin-like growth factor-1; ITT, insulin tolerance test; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin.

deficiencies (9, 32, 34), but in our study, there was no difference between SS-LCH and MS-LCH. Our prevalence was also more than the approximately 30% reported in Erdheim Chester Disease (ECD), which is another histiocytic infiltrative disorder (7), even when a complete assessment was done systematically (35, 36). Our high prevalence was also attributable to CO LCH in which almost three quarters of the patients had DI. One previous study of 70 CO LCH patients found a 10-year cumulative incidence of DI of 20% (37).

As shown in this study, the absence of the physiological bright spot in the posterior pituitary is common in patients with DI and could be idiopathic or secondary to ECD or LCH (34, 35, 38, 39). For the patients with DI who still had a visible bright spot, it is likely that, depending on the conclusion of the neuroradiologist, the fat of the bony posterior wall of the sella turcica was falsely considered as the posterior pituitary bright spot. The second most common MRI abnormality is infundibular or pituitary stalk thickening (31, 38, 39), but a normal pituitary MRI scan is not sufficient to rule out pituitary impairment. We did not find any neurodegenerative complications but pituitary gland abnormalities are a known risk factor (40).

The prevalence of APD in our two subgroups was also higher than the 8.7–33% reported previously in LCH or ECD (10, 11, 29, 34, 35, 41, 42), but very few studies have reported patients with a complete evaluation, which means that the prevalence of some deficiencies is probably underestimated. Our results suggest, contrary to recommendations (1, 2), that a complete hypothalamo-pituitary evaluation should be performed in all LCH patients, especially as 15.8% of our patients in the subgroup of completely evaluated and 12% in the second group had ED but they had no suspected endocrine manifestation before evaluation. APD is almost never associated with DI. Older age at the diagnosis of LCH or the presence of low risk clinical forms and fewer reactivation episodes seem to be the main predictors of a higher risk of developing APD when DI is already diagnosed (43).

The most common APD was GHD, followed by gonadotropin deficiency, hyperprolactinemia and thyrotropin deficiency in our two subgroups. Our findings are similar to those in the LCH and ECD literature (9, 10, 29). But we cannot discard that GH deficiency has been probably overdiagnosed especially in the four obese adult patients in whom it was isolated or in children due to the lack of a confirmatory testing and auxological data. As previously observed, the pediatric guidelines recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD (44).

As found in other LCH and ECD studies (10, 35), the prolactin levels were moderately elevated, which can be attributed to pituitary stalk infiltration (1).

All of our patients with corticotropin deficiency reported a history of corticosteroid treatment, and we thus considered that they were deficient because of the treatment rather than the LCH.

We found no primary hypothyroidism (other than autoimmune hypothyroidism), but thyroid involvement is known to be involved in LCH (29, 45, 46, 47).

The skeletal status of our population was difficult to ascertain on the basis of BMD alone because of the young age of our patients and because we did not systematically perform an active research for vertebral fractures (48). But it is known that this population has multiple risk factors of osteoporosis (proinflammatory cytokines, APD and hormonal replacement, and corticosteroid therapy, non-condensing bone lesions).

As described in other studies of patients with LCH or ECD, EDs can appear progressively during follow-up and generally are definitive (9, 35, 37, 42). It is thus important that all LCH patients be monitored regularly using established endocrine investigational protocols to detect further pituitary hormone deficiencies or metabolic alterations.

The prevalence of the BRAF V600E mutation in LCH ranges from 38 to 60% (49, 50, 51). This frequency was probably low because this test was performed only in a few patients.

In summary, we have confirmed that endocrine manifestations are extremely frequent in a large cohort of LCH patients who were evaluated systematically. Thus, we recommend a complete endocrine evaluation in each LCH patient and further regular monitoring.

Our recommendations for the endocrine assessment and monitoring protocol in patients with LCH are presented in Table 5.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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